Understanding the Late Effects of Cancer Treatment:

A Medical Oncologist's Perspective

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Overview of Presentation

- Where have we been? *OR* What do we know?
- Where are we now? *OR* At least survivorship research is on the table for discussion.
- Where should we be going? *OR* Personal thoughts about future research efforts.

General Considerations

- Risk of late effects depends on the tissue and age of patient at time of treatment
- Late effects are dose and modality specific (e.g., surgery, radiation, chemotherapy)
- Combined modality therapy can have additive risks

Tissues at Risk for Late Toxicity

- Bone/soft tissues
- Cardiovascular
- Dental
- Endocrine
- Gastrointestinal
- Hepatic
- Hematological
- Immune system
- Nervous system
- Neuropsychologic
- Ophthalmologic
- Pulmonary
- Renal
- Reproductive

Case Examples

- 20 y.o. male who received combined modality therapy for Wilms tumor at age 5, including radiotherapy given to chest for lung metastases
  - cc: hemiatrophy of right chest wall musculature, scoliosis, decreased lung volumes

Case Examples

- 53 y.o. female with a history of breast cancer diagnosed at age 40 treated with surgery and adjuvant chemotherapy → premature menopause
  - cc: multiple atraumatic fractures, marked reduction in bone mineral density

Case Examples

- 35 y.o. male with history of Wilms tumor left kidney treated with surgery and radiation therapy at age 7 years; basal cell carcinoma left abdominal wall at age 28
  - cc: needs health insurance coverage; has change in bowel habits and needs some tests

Case Examples

- 28 y.o. female with history of treatment with mantle irradiation for stage II Hodgkin's disease at age 18
  - cc: lump in right breast which is biopsied and shows breast cancer

Case Examples

- 75 y.o. male with history of high grade lymphoma treated with CHOP chemotherapy 2 years ago
  - While traveling in Japan with his daughter, he becomes exhausted and short of breath with exertion
  - He returns home and is found to have a cardiac ejection fraction of 35%; his symptoms improve after treatment for congestive heart failure

What can we learn from these case examples?

- Late effects can occur shortly after treatment or many years later
- Patients of all ages can be affected
- Degree of risk to individual patients cannot be predicted
- Second cancers are the most life-threatening late effect, but other disabling conditions occur

Understanding the potential toxicities of each treatment modality is critical if we are to develop preventive strategies!!

Late Effects of Surgery

- Limb Amputation: functional changes, cosmetic deformity
- Abdominal surgery: intestinal obstruction from adhesions, short bowel syndrome
- Lymphadenectomy: lymphedema
- Splenectomy: immune dysfunction, sepsis
- Pelvic surgery: impotence, incontinence

Late Effects of Chemotherapy

Renal	Cisplatin Methotrexate Nitrosoureas	Renal Failure Mg++ wasting
Genitourinary	Cyclophosphamide	Hemorrhagic Cystitis, Bladder fibrosis

Late Effects of Chemotherapy

Bone	Steroids	Avascular necrosis
Cardiac	Anthracyclines Cyclophosphamide	Cardiomyopathy CHF
Pulmonary	Bleomycin Methotrexate BCNU	Pulmonary fibrosis Intersitial pneumonitis
Ophthalmic	Steroids	Cataracts

Late Effects of Chemotherapy

CNS	Methotrexate	Structural changes, Hemiplegia, Seizures
Peripheral Nervous System	Cisplatin Vinca Alkaloids Paclitaxel	Peripheral neuropathies, Hearing loss

Late Effects of Chemotherapy

Hematological	Alkylating agents Topo II inhibitors	Myelodysplasia, AML
Gastrointestinal	Methotrexate BCNU	LFT abnormalities, Hepatic fibrosis or cirrhosis
Gonadal	Alkylating agents Procarbazine	Sterility Early menopause

Late Effects of Radiotherapy

All tissues	Second malignancies
Bone & Soft Tissues	Abnormal growth, short stature; atrophy, deformity, fibrosis, osteonecrosis
Dental/Oral Health	Poor enamel & root formation; dry mouth

Late Effects of Radiotherapy

CNS	Neuropsychological deficits; structural changes; hemorrhage
Hematological	Cytopenias Myelodysplasia
Renal	Hypertension Decreased GFR
Genitourinary	Bladder fibrosis, strictures

Late Effects of Radiotherapy

Ophthalmologic	Cataracts Retinopathy Keratoconjunctivitis
Cardiovascular	Pericardial effusion Constrictive pericarditis Coronary artery disease
Pulmonary	Pulmonary fibrosis Decreased lung volumes

Late Effects of Radiotherapy

Gastrointestinal	Malabsorption Intestinal stricture Abnormal LFTs
Endocrine Pituitary Thyroid Gonadal	GH & other deficiencies Hypothyroidism, nodules Sterility, Leydig cell dysfunction, ovarian failure, premature menopause

Appreciation to Pediatric Oncology Researchers…

- You have taught us much about the late effects of cancer treatment---you lead the way
- Your high survival rates and commitment to clinical trials are a model and a resource for survivorship research!

Some late effects in adults may be less life-threatening, but more troubling….

Estrogen Deficiency: Short Term Effects

- Vasomotor symptoms, vaginal dryness, mood changes, sleep disturbance
- Musculoskeletal complaints, joint pains, skin changes
- Urinary incontinence (women)
- Sexual changes, dyspareunia (women)

Oncology Treatments that Exacerbate this Problem

- SERMS
- Anti-estrogens, ER degradation agents
- Aromatase Inhibitors
- GnRH analogs (in both men and women)
- Oophorectomy
- Orchiectomy

E-mail from a patient, 3 months after starting AI therapy after 5 years of Tamoxifen

"It has been several months since I started taking Femara. Although I do want to continue taking it and not take any chances with a cancer recurrence, I have encountered some problems. I am experiencing constant pain in my muscles, joints etc., as if my body was continuously sore from strenuous exercise. The hardest times are in the morning and in the late afternoon, and I am usually very tired in the afternoon as well. I feel much better after exercise, but often I do not have enough energy or willpower after work to go to the gym. Instead I go to my bedroom and sleep. All together, this is not me and I want to do something to change it."

Estrogen Deficiency: Late Effects

- Osteoporosis and fracture (men and women)
- Infertility (women)
- Lipid changes…? Cardiac risks

And where are we now?

- A decade of RFA supported research funded by the NCI
- An NCI Office of Cancer Survivorship
- Several NCI sponsored conferences such as this
- A developing body of descriptive research
- Multi-dimensional health-related QOL as a short & long-term outcome

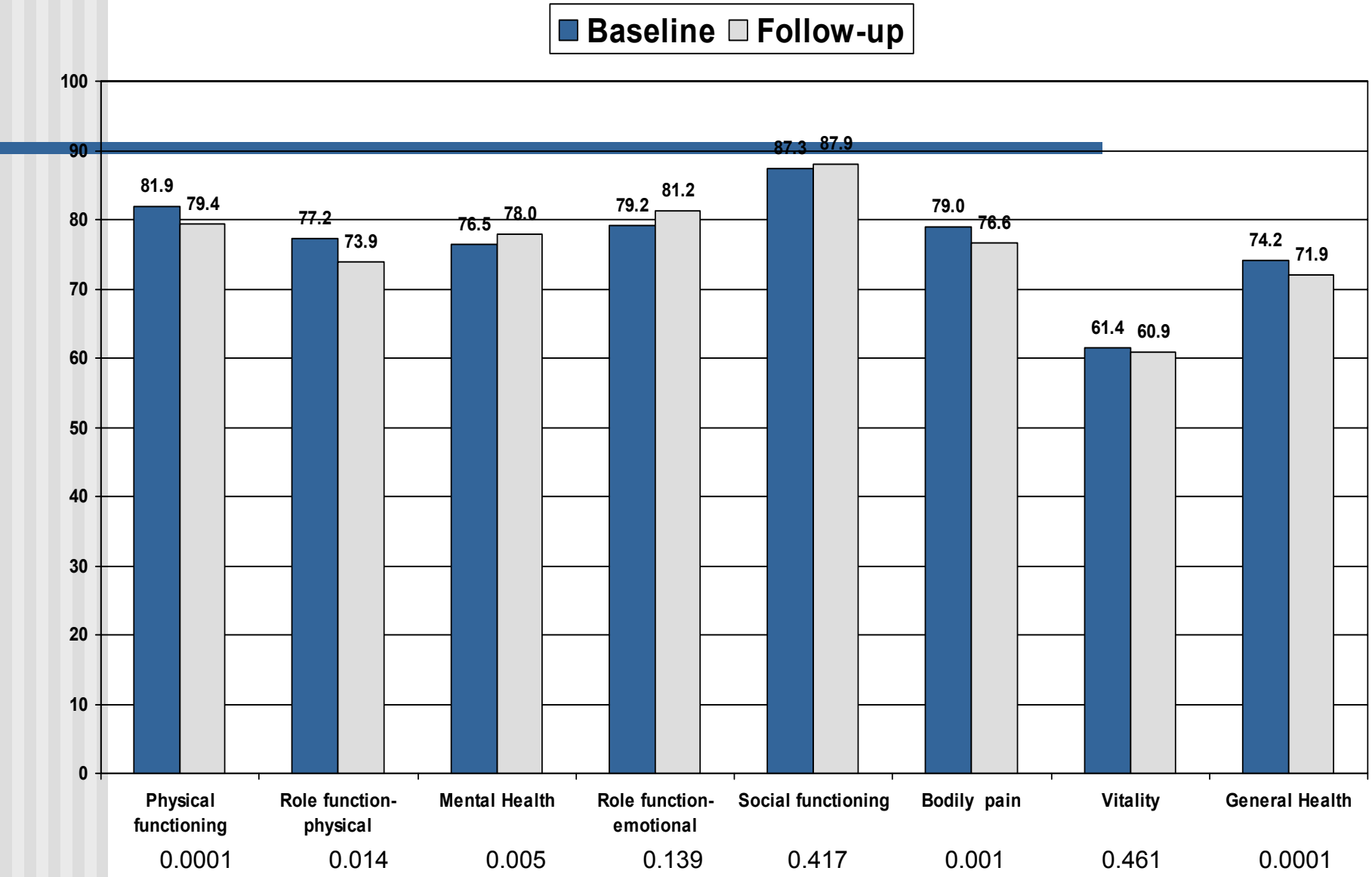
QOL in Long-term, Disease-Free, Breast Cancer Survivors: A Follow-up Study

Longitudinal Cohort Study

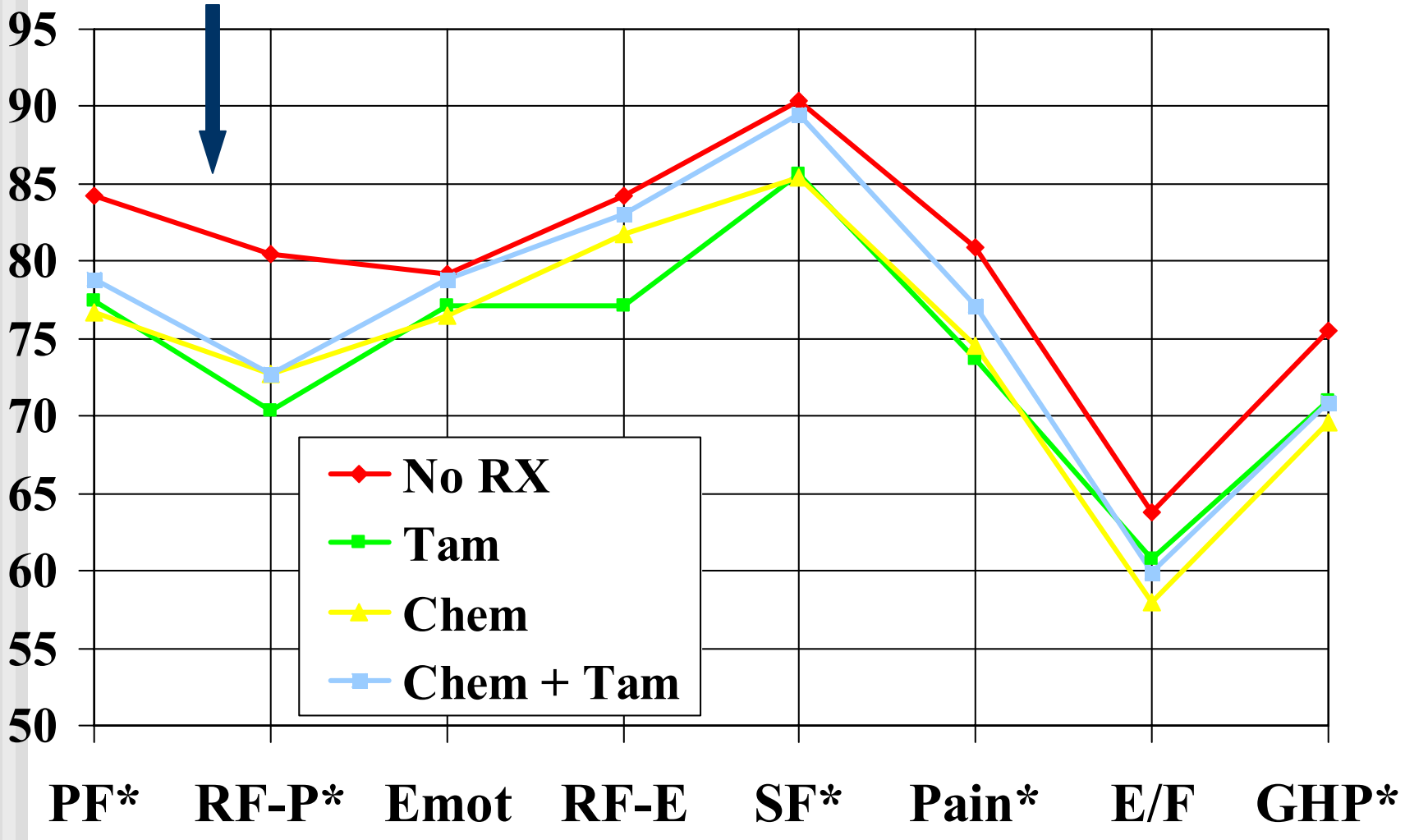
- 763 early stage breast cancer patients assessed at two times
  - Baseline: between 1 and 5 years after dx
  - Follow-up: between 5.0 and 9.5 years after dx
- Use of standardized measures of QOL, depression, mood, sexual functioning

Ganz et al., JNCI, January 2, 2002

SF-36 Health Profile Scores

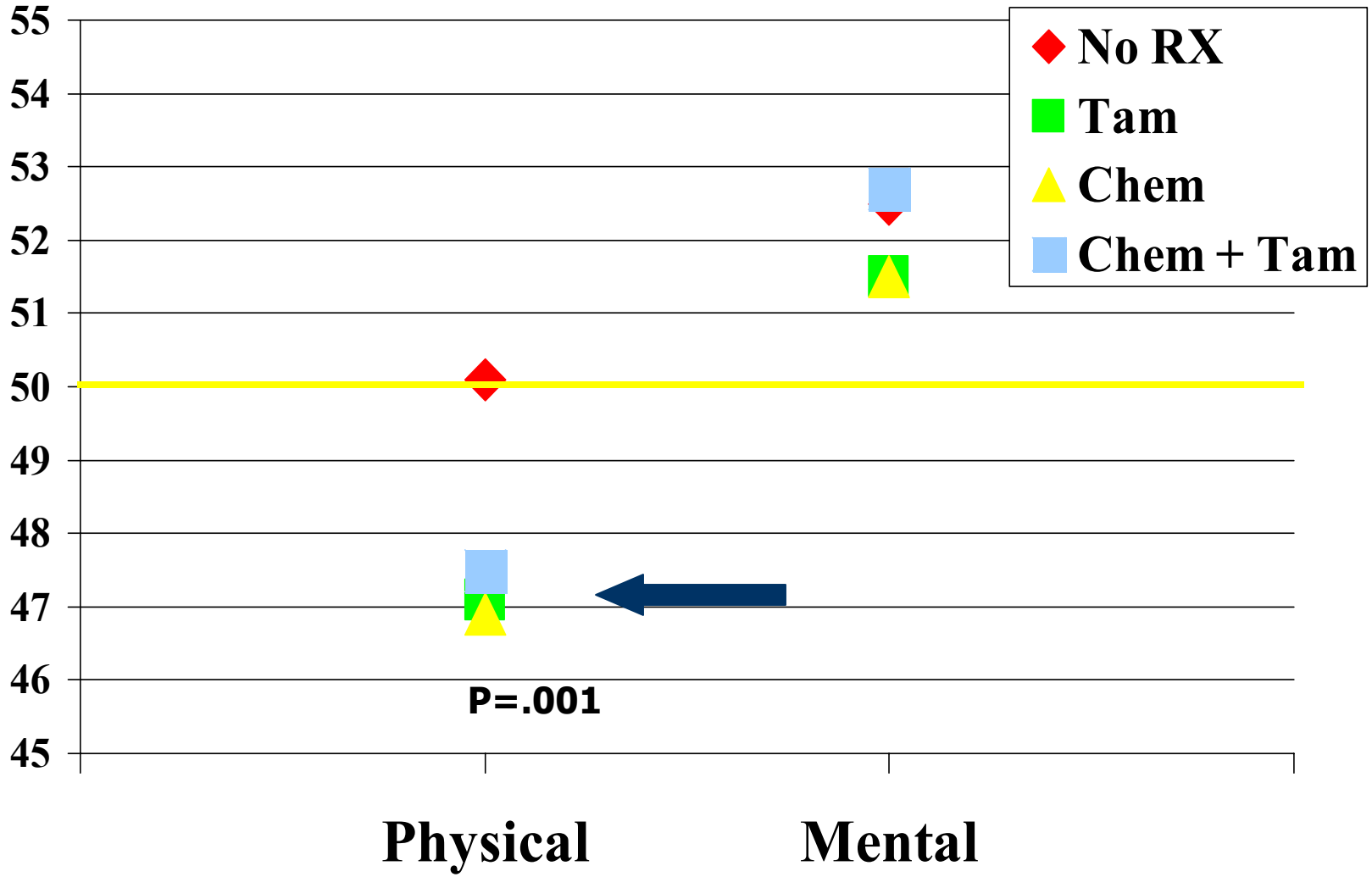


SF-36 Scores According to Adjuvant Treatment



Long Term Survivors

MOS-SF-36 Component Scales



Late Cardiac Effects of Adjuvant CMF vs. CAF in Women with Node Negative Breast Cancer Treated on SWOG 8897: Initial Results from SWOG 9342

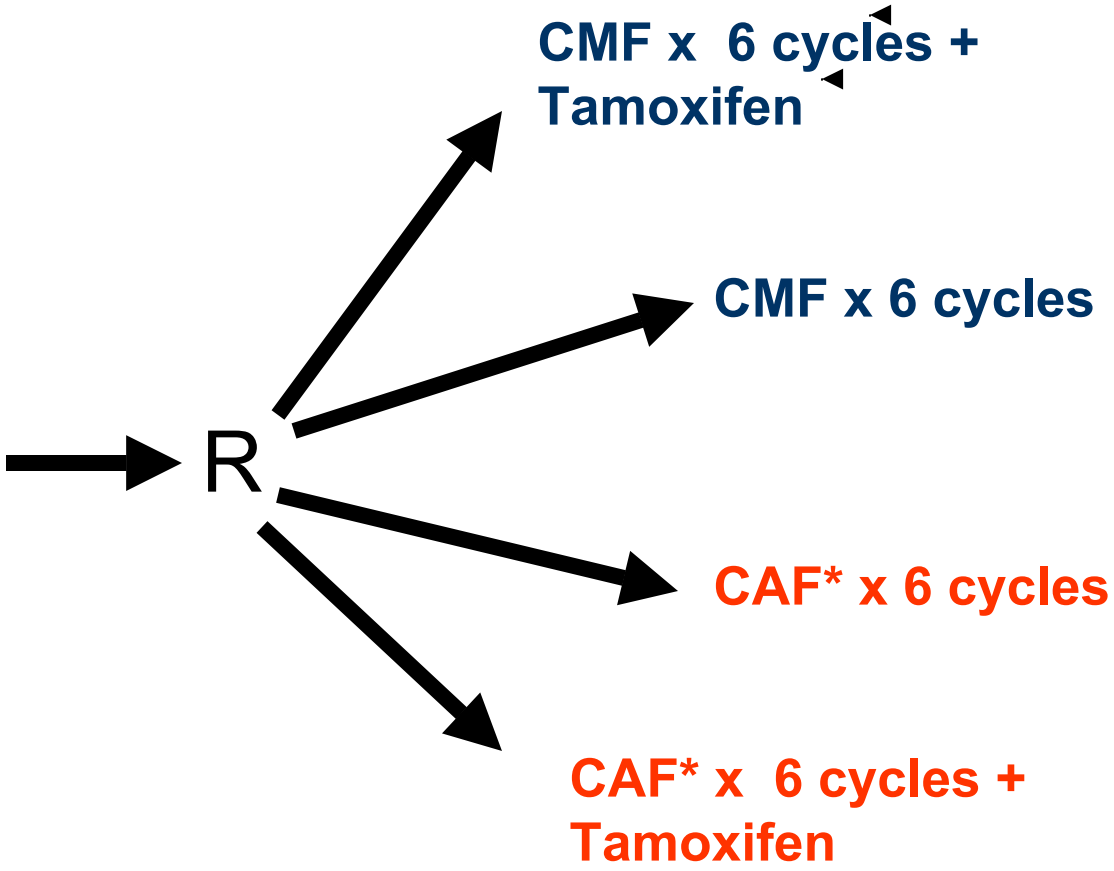
P. A. Ganz, S. J. Green, L. Hutchins,
S. Martino, J. Gralow, R. Livingston,
K. Albain for the Southwest Oncology Group

San Antonio Breast CA meeting, 2002

SWOG 8897 Schema

Stratification Factors

1. Hormone receptors
2. Timing of surgery
3. Menopausal status

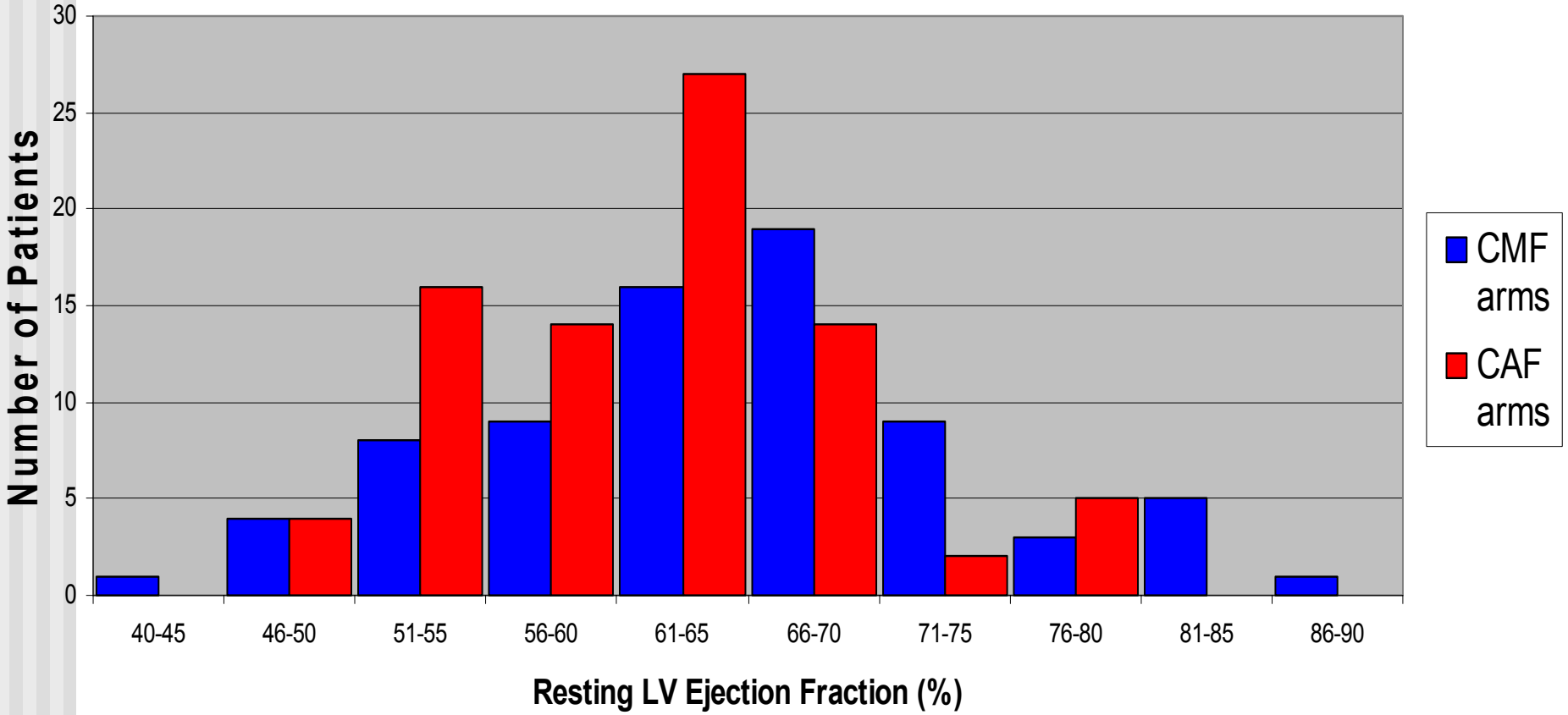


* Total dose of doxorubicin = 360 mg/m^2

MUGA Scan Results at 5-8 yrs

	CMF Arm	CAF Arm	P-value
LV Ejection Fraction < 50%	7%	5%	NS
Mean LV Ejection Fraction	64.9% (44-89 range)	61.2% (47-79 range)	0.006

Resting LV Ejection Fraction (%) by Treatment



And persistent **FATIGUE**…

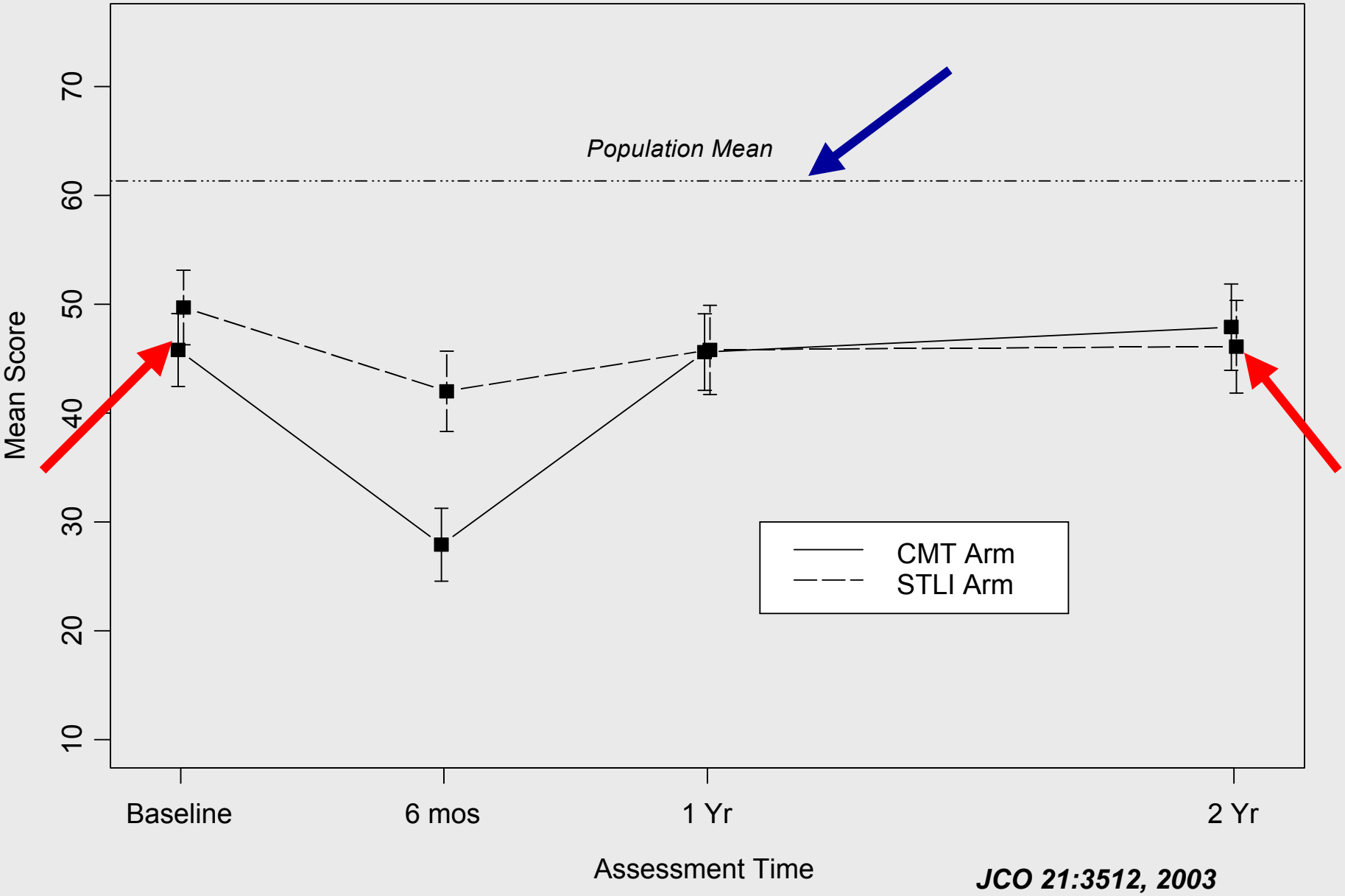
- Another common complaint in survivors
- Is it from the disease or the treatment?

Predictors of Vitality (Energy/Fatigue) in Early Stage Hodgkin's Disease: Results from SWOG 9133

P.A. Ganz, C.M. Moinpour, S. McCoy, D.K. Pauler, O.W. Press, R.I. Fisher

ASCO, 2004

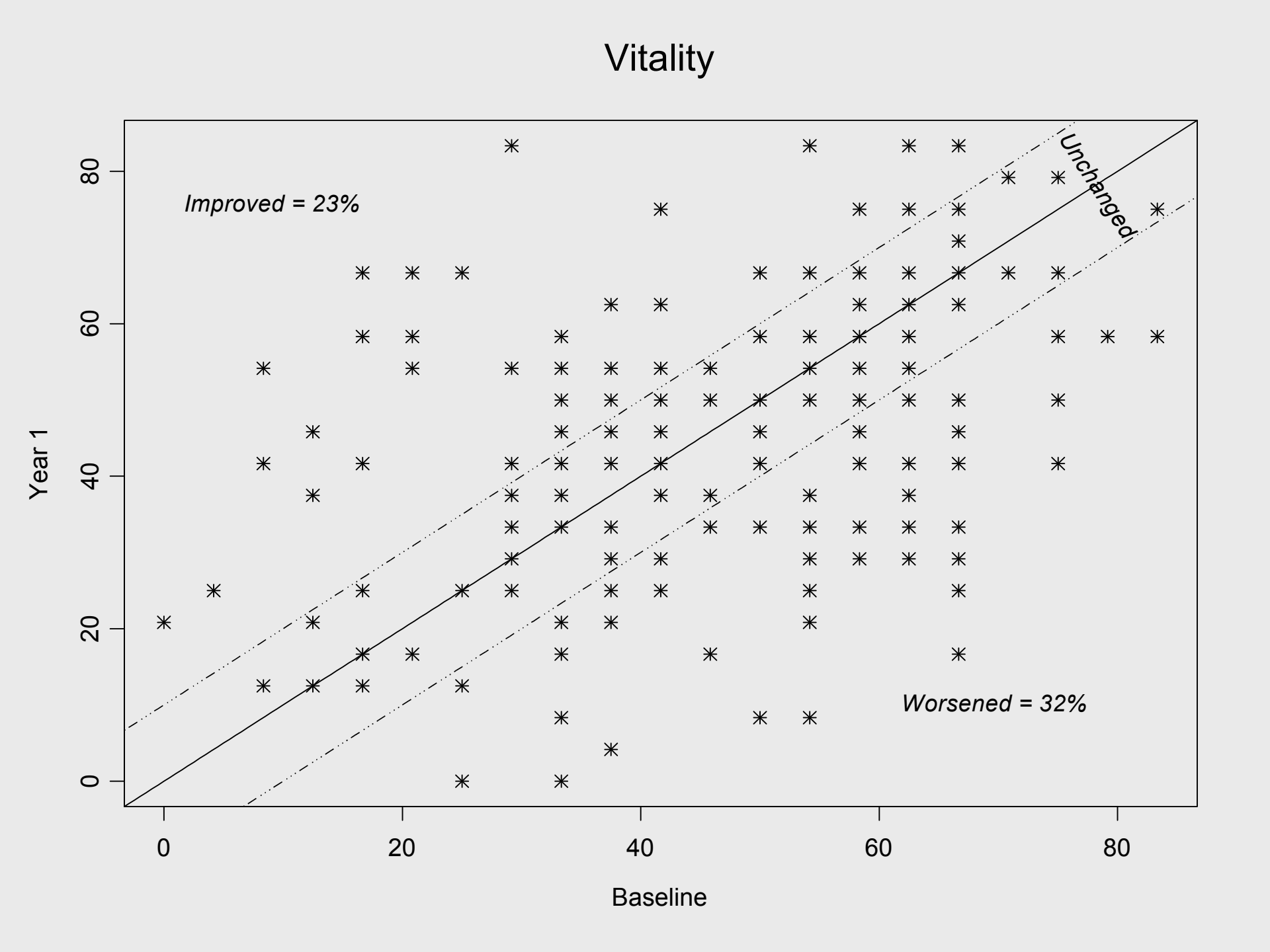
Vitality Scale



JCO 21:3512, 2003

Relationship Between Vitality at Baseline & 1 Year

- Correlation = .41
- Classified patients
  - *Improved*, *No Change*, *Worsened*
- Clinically significant change = ≥ 10 points
  - 10% change on 0 to 100 scale (scale range)
  - Reflective of a moderate effect size (Cohen, 1988; Sloan et al., 1998)
- *No change* boundaries + or - <10 points
  - *Improved* above boundary area
  - *Worsened* below boundary area


Vitality
Improved = 23%
Unchanged
Worsened = 32%
Year 1
Baseline
0
20
40
60
80

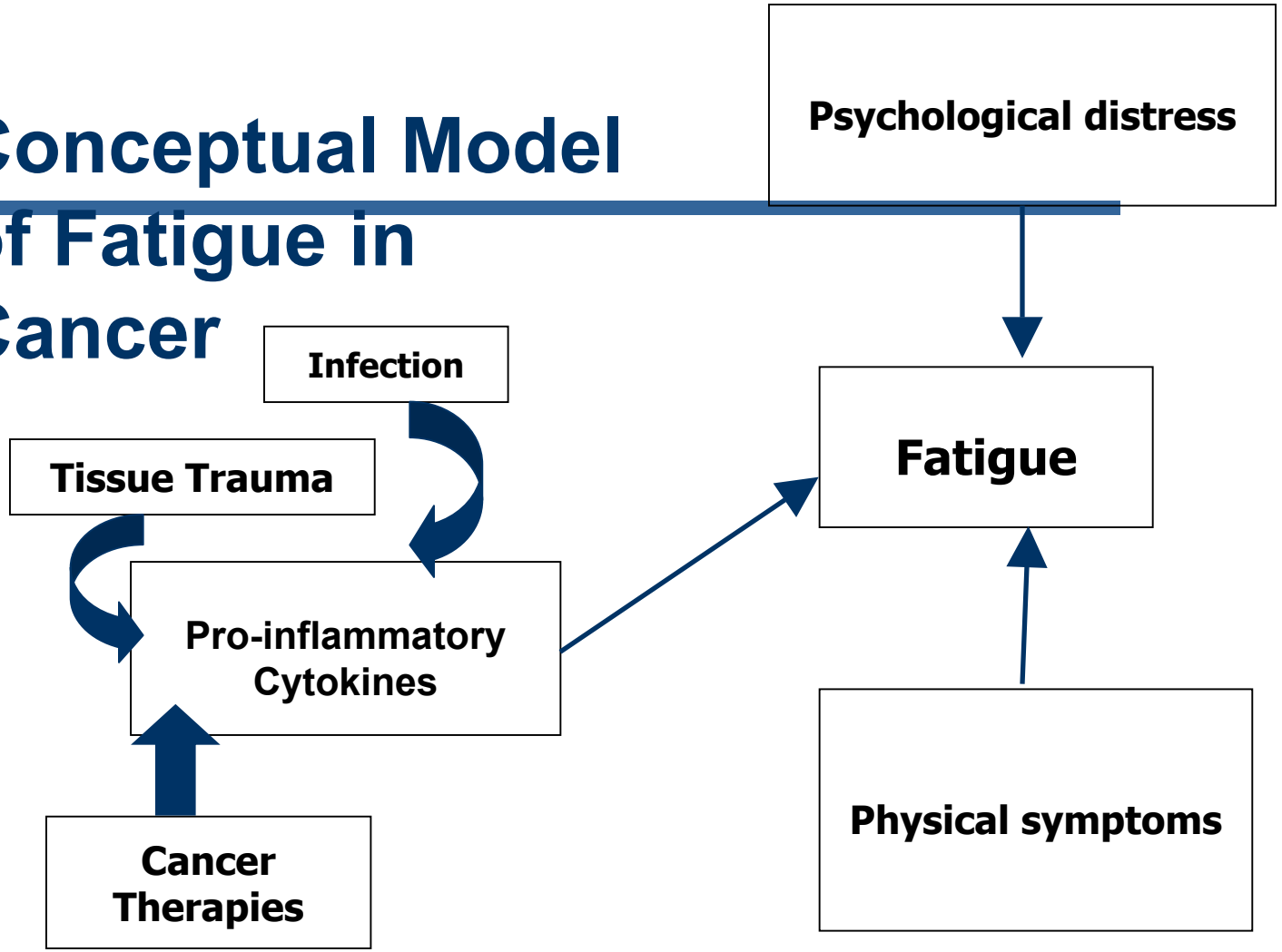
Conclusions

- In early stage HD, disease and treatment factors are not related to decreased vitality *initially* or in *follow-up*
- It is possible that elevated levels of pro-inflammatory cytokines, as part of the underlying disease, may play a role
- Further research is necessary to understand the mechanisms of fatigue in HD patients

Where should we be going?

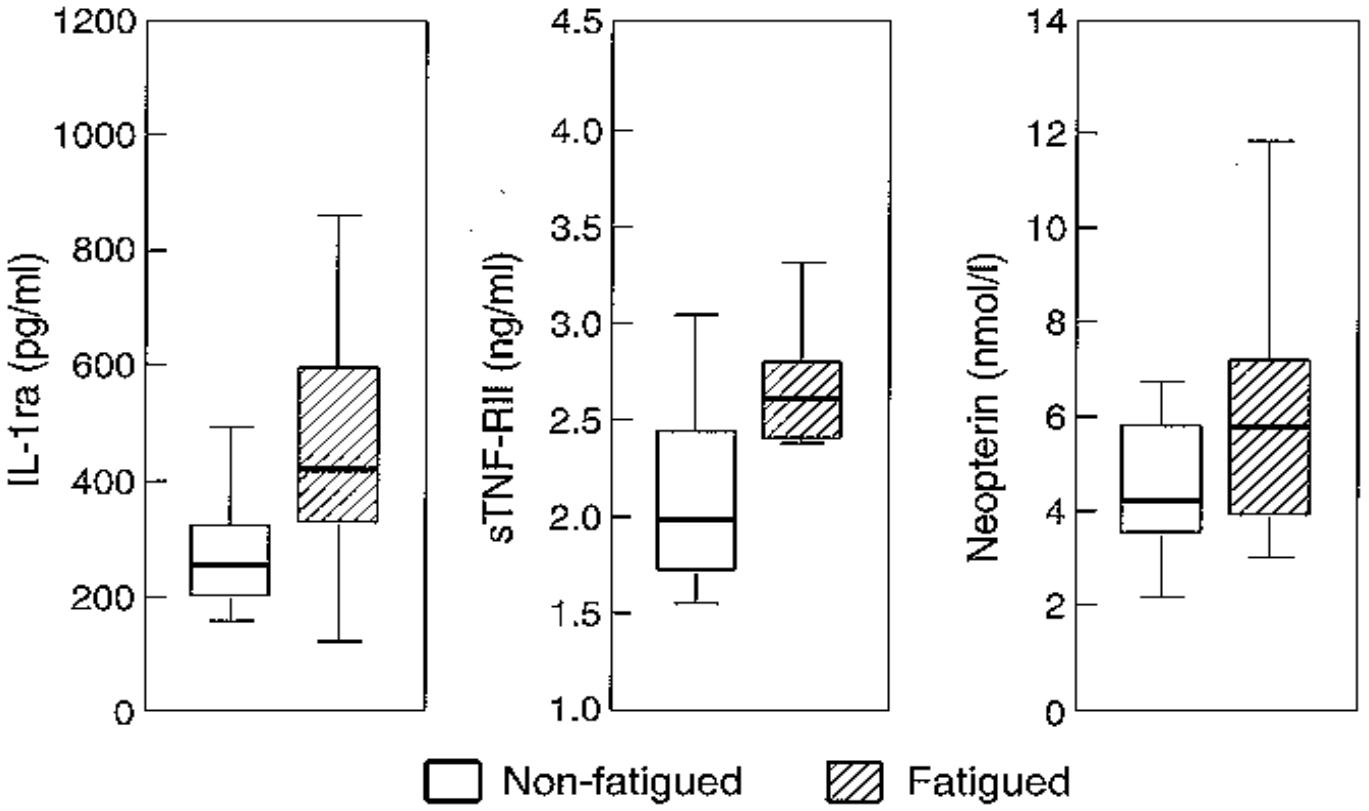
- Need to understand the mechanisms of more common late effects
- Must reduce or prevent the late serious toxicities of treatments
- Need for multidisciplinary, prospectively designed studies with long-term follow-up

Conceptual Model of Fatigue in Cancer



Bower & Ganz, 2004

Fatigue and Immune Markers in Breast Ca Survivors



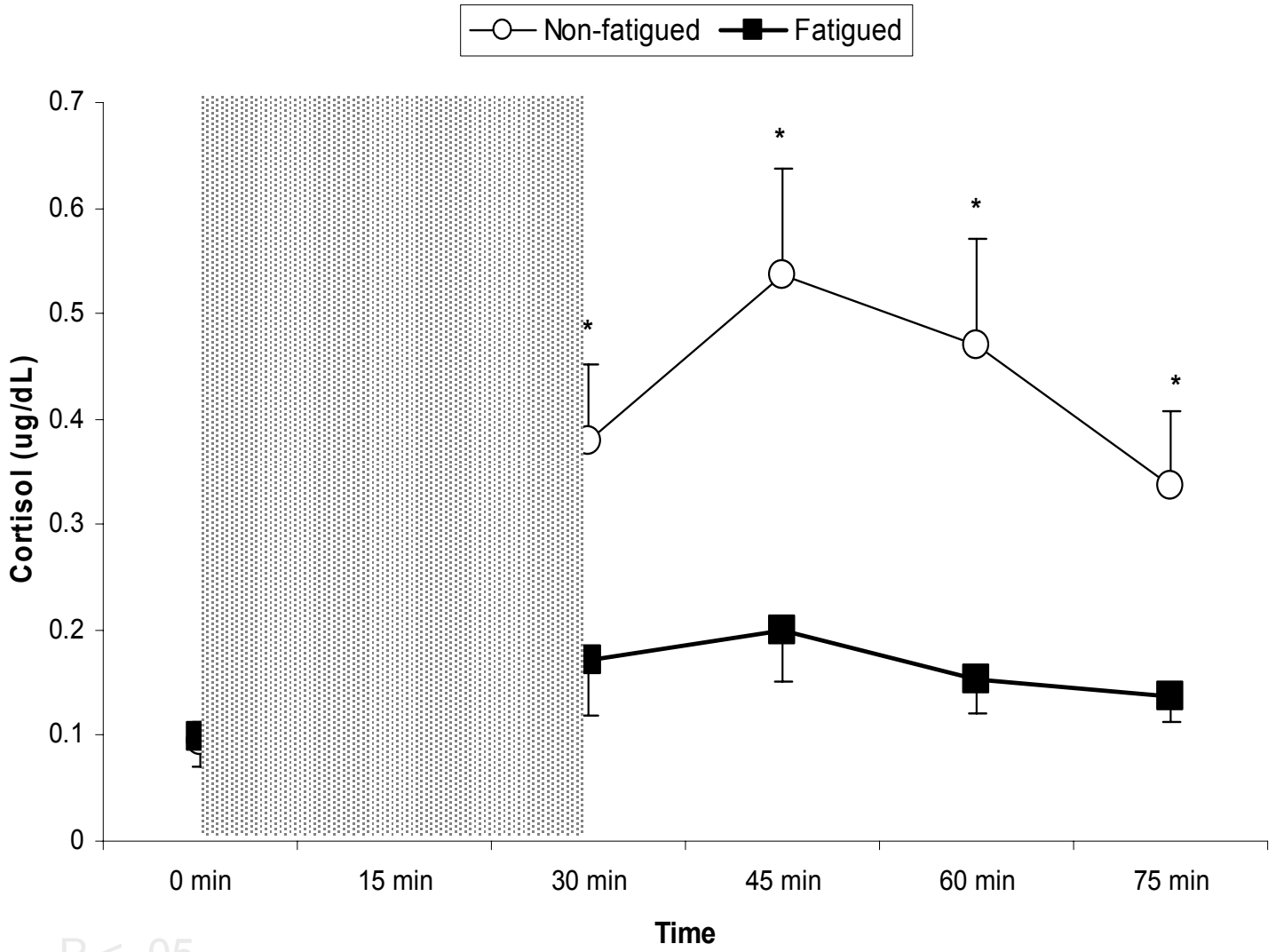
Bower, et al. Psychosomatic Med, 2002

Cortisol

	Non-fatigued	Fatigued
Cortisol (µg/dl)	14.0 (3.2)	11.9 (3.7)*

- Cortisol *negatively* correlated with immune activation markers in non-fatigued group
- Cortisol *positively* correlated with immune activation markers in fatigued group

Cortisol Response to Experimental Stress According to Fatigue Status



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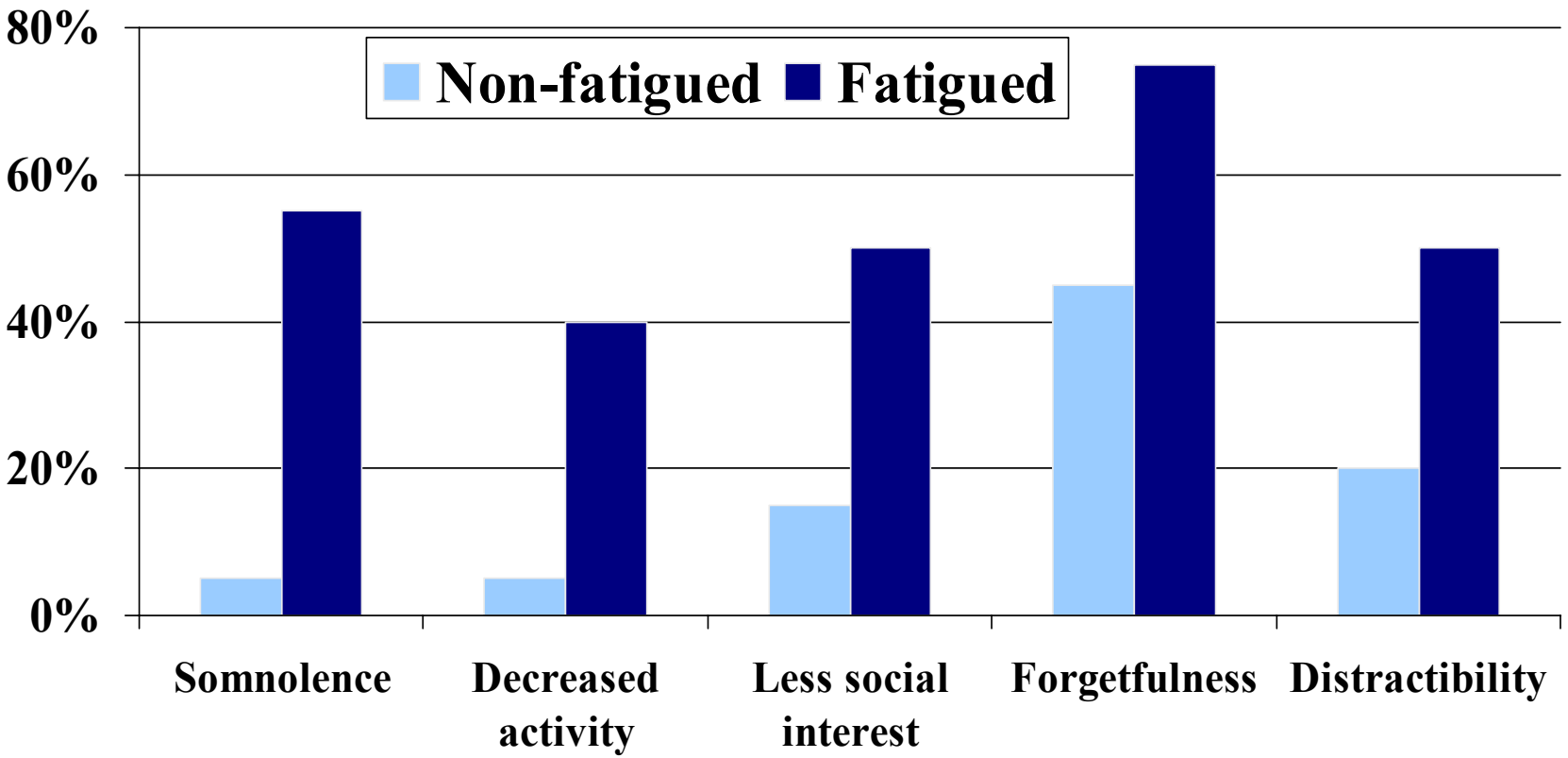
Fatigue and Sickness Behaviors



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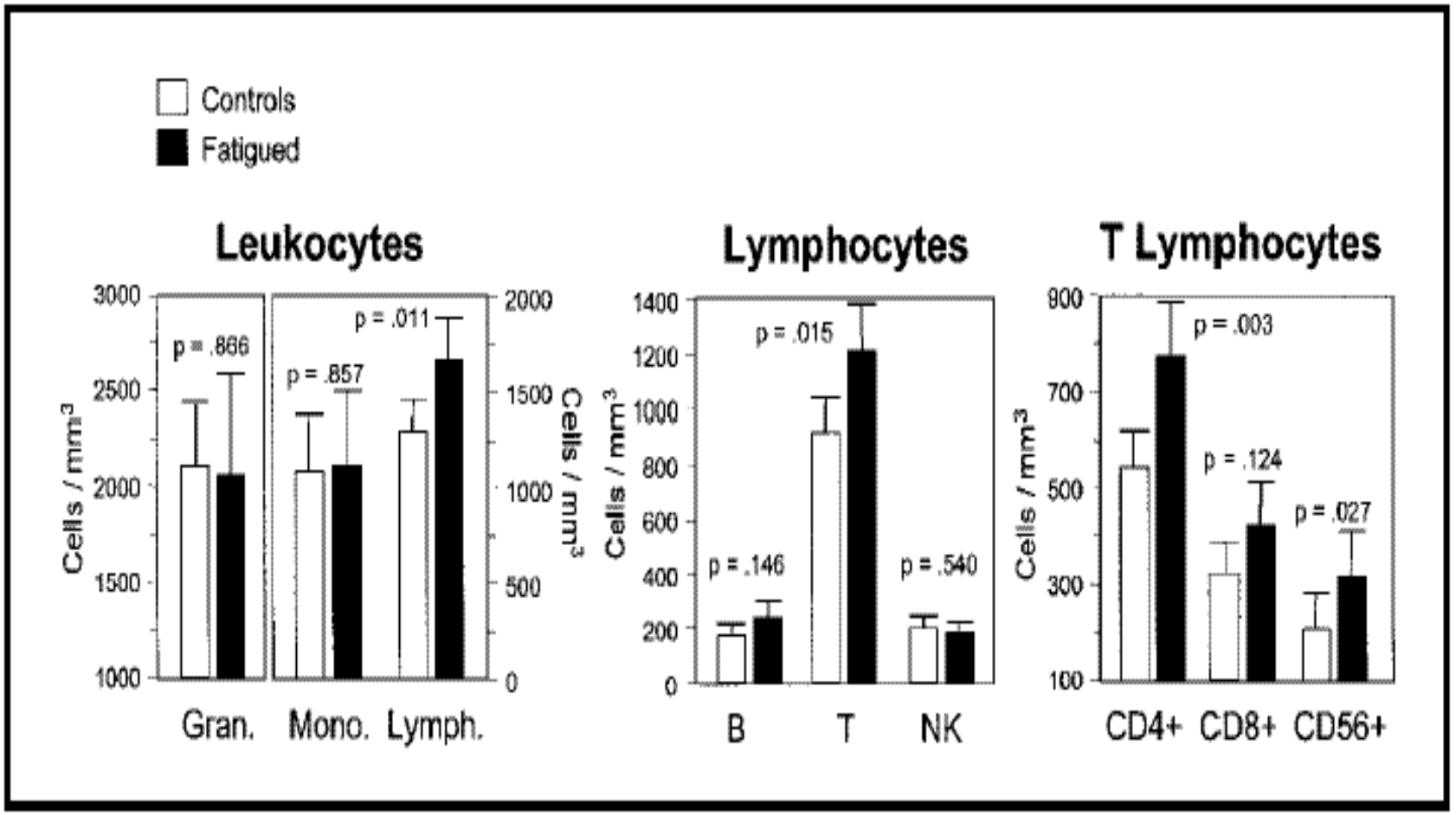
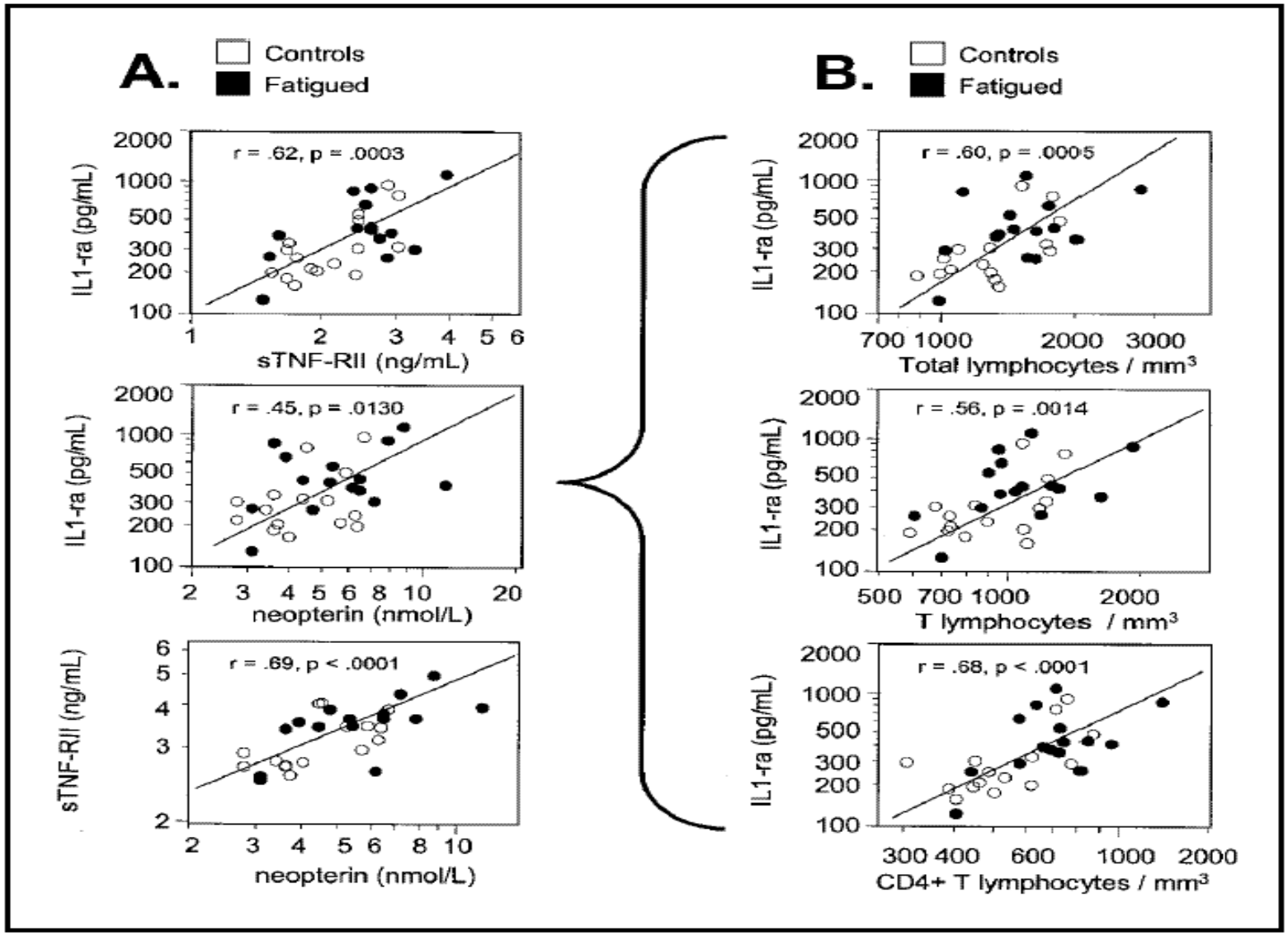
Distribution of leukocytes in fatigued & non-fatigued Breast Cancer Survivors



Bower, et al., JNCI 2003

Relationships between soluble inflammatory markers & leukocyte distributions in breast cancer survivors

Bower, et al., JNCI 2003



How to go forward?

- Develop centers of excellence to study late effects from a multidisciplinary perspective
- Validate observations from individual laboratories in the cooperative group setting, specifically in controlled trials
- Test preventive interventions along with treatments in the cooperative group setting

Treatment decisions must weigh the benefits against the harms…..

In spite of the uncertainties, there can still be a good life after cancer…..